Frailty is associated with decline in health-related quality of life of patients treated for head and neck cancer

de Vries, Julius; Bras, Linda; Sidorenkov, Grigory; Festen, Suzanne; Steenbakkers, Roel J H M; Langendijk, Johannes A; Witjes, Max J H; van der Laan, Bernard F A M; de Bock, Geertruida H; Halmos, Gyorgy B

Published in:
Oral Oncology

DOI:
10.1016/j.oraloncology.2020.105020

Oral Oncology 111 (2020) 105020

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Frailty is associated with decline in health-related quality of life of patients treated for head and neck cancer

Julius de Vries[a,*,1], Linda Bras[a,1], Grigory Sidorenkov[b], Suzanne Festen[c], Roel J.H.M. Steenbakkers[d], Johannes A. Langendijk[d], Max J.H. Witjes[e], Bernard F.A.M. van der Laan[a,f], Geertruida H. de Bock[b], Gyorgy B. Halmos[a]

[a] University of Groningen, Department of Otorhinolaryngology, Head and Neck Surgery, University Medical Center Groningen, Groningen, the Netherlands
[b] University of Groningen, Department of Epidemiology, University Medical Center Groningen, Groningen, the Netherlands
[c] University of Groningen, Department of Geriatric Medicine, University Medical Center Groningen, Groningen, the Netherlands
[d] University of Groningen, Department of Radiation Oncology, University Medical Center Groningen, the Netherlands
[e] University of Groningen, Department of Oral and Maxillofacial Surgery, University Medical Center Groningen, Groningen, the Netherlands
[f] Haaglanden Medical Center, Department of Otorhinolaryngology, Head and Neck Surgery, The Hague, the Netherlands

ARTICLE INFO

Keywords:
Head and neck cancer
Frailty
Geriatric screening
Comorbidity
Quality of life
Functioning

ABSTRACT

Objective: To determine the effect of frailty on Health Related Quality of Life (HRQoL) after treatment for Head and Neck Cancer (HNC).

Materials and methods: Patients were prospectively included in OncoLifeS, a data-biobank. Before treatment, patients underwent geriatric screening, including the Groningen Frailty Indicator (GFI) and Geriatric 8 (G8). Patients' HRQoL was measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) at three, six, twelve and twenty four months after treatment. Linear mixed models were used for statistical analysis. All models were adjusted for baseline HRQoL values, relevant confounders at baseline and yielded estimates (β), 95% confidence intervals and p-values.

Results: 288 patients were included. The mean age was 68.4 years and 68.8% were male. During follow-up, 84 patients had tumor recurrence and 66 died. Response to EORTC-QLQ-C30 ranged from 77.3% to 87.8%. Frail patients, defined by GFI, had significantly worse Global Health Status/Quality of Life (GHS/QoL) ($\beta = -8.70(-13.54;-3.86)$, $p < 0.001$), physical functioning ($\beta = -4.55(-8.70;-0.40)$, $p < 0.032$), emotional functioning ($\beta = -20.06(-25.65;-15.86)$, $p < 0.001$), and social functioning ($\beta = -8.44(-13.91;-2.98)$, $p < 0.003$) three months after treatment compared to non-frail patients. Furthermore, frail patients had a significantly worse course of GHS/QoL ($\beta = -7.47(-11.23;-3.70)$, $p = 0.001$), physical functioning ($\beta = -3.28(-6.26;-0.31)$, $p = 0.031$) and role functioning ($\beta = -7.27(-12.26;-2.28)$, $p = 0.005$) over time, compared to non-frail patients. When frailty was determined by G8, frailty was significantly associated with worse GHS/QoL ($\beta = -6.68(-11.00;-2.37)$, $p = 0.003$) and emotional functioning ($\beta = -5.08(-9.43;-0.73)$, $p = 0.022$) three months after treatment.

Conclusion: Frail patients are at increased risk for decline in HRQoL, and further deterioration during follow-up after treatment for HNC.

Introduction

With the incidence of cancer and specifically the proportion of elderly with cancer rising, oncologists may increasingly encounter the geriatric syndrome of frailty [1]. Frailty results from the heterogenic process of aging, leaving great diversity in populations with respect to physical, functional, psychological and social status, and is defined as *'a state of increased vulnerability to poor resolution of homeostasis after a stressor event, which increases the risk of adverse outcomes'* [2]. Often, chronological age is not very representative of a patient's biological age. One of the populations that is thought to be very frail are patients with Head and Neck Cancer (HNC). In this population, functional and cognitive impairment, depressive symptoms and social isolation have shown to be highly prevalent [3]. The burden of frailty in HNC patients

* Corresponding author at: PO box 30.001, HPC BB20, 9700RB Groningen, The Netherlands.
E-mail address: j.de.vries01@umcg.nl (J. de Vries).
[1] Authors contributed equally to the study.

https://doi.org/10.1016/j.oraloncology.2020.105020
Received 10 June 2020; Received in revised form 12 September 2020; Accepted 17 September 2020

is higher than in patients with other solid malignancies [4]. Probably, general symptoms secondary to tumor extension and location, such as weight loss and malnutrition, contribute to this [5]. Additionally, patient related factors such as lifelong tobacco and alcohol abuse, which are etiological factors for HNC, increase frailty status as well [6,7].

For head and neck oncologists, this leads to a challenging clinical problem. On the one hand, intensive, often multimodal, treatment is indicated; on the other hand, patients may be vulnerable with multiple comorbidities, polypharmacy, functional and psychosocial restrictions. This makes decision making challenging. Ideally, by determining the biological age (i.e. frailty), undertreatment of fit elderly and overtreatment of frail young patients should be prevented. The gold standard to assess frailty is a Comprehensive Geriatric Assessment (CGA) by a geriatrician [8]. Because of its time consuming nature, burden for the patient and limited health care capacity, screening tools have been developed to select patients that need CGA [9].

In HNC, frailty has already been associated with increased frequency and severity of postoperative complications, prolonged length of hospital stay, increased readmission rates and worse overall survival [10]. Although these outcome measures are all clinically relevant, they do not represent the perspective of the patient. Older patients have different priorities regarding treatment outcome than their younger counterparts; e.g. Health Related Quality of Life (HRQoL) may be considered more important than survival in decision making [11–13].

Long-term HRQoL as reported by patients is increasingly considered a valuable outcome measure for cancer treatment. Previous studies showed that frailty is associated with worse HRQoL in other oncological cohorts [14–17]. However, this has never been investigated specifically in HNC patients. A more accurate prediction of patient-rated HRQoL may be of help in decision making and management of expectations. In the present prospective study, we investigated how frailty affects HRQoL shorty after treatment for HNC, and how frailty affects the course of HRQoL during long-term follow-up after treatment.

Material and methods

Study design

The present study is a prospective observational cohort study with two years of follow-up. All patients were enrolled in OncoLifeS, a prospective oncological data-biobank at the (UMCG) [18]. OncoLifeS has been approved by the local Medical Ethical Committee and the study protocol was approved by the OncoLifeS scientific board.

Study population

Between October 2014 and May 2016, all consecutive patients referred to the UMCG with a mucosal, salivary gland or complex cutaneous malignancy (giant basal cell carcinoma, squamous cell carcinoma stage II or higher, melanoma, Merkel cell carcinoma and neck metastasis of any cutaneous malignancy, requiring major surgery and/or radiotherapy) of the head and neck were asked to participate in OncoLifeS and were included after obtaining written informed consent (Fig. 1). Patients were seen at the outpatient clinics of the department of Otorhinolaryngology, Head and Neck Surgery, and the department of Oral and Maxillofacial Surgery. Patients were treated according to (inter)national guidelines and discussed within our multidisciplinary head and neck tumor board. Exclusion criteria were palliative treatment, non-standard treatment (e.g. in the scope of other clinical trials) and missing baseline data on HRQoL (Fig. 1). As the burden of frailty is expected to be relatively high in young HNC patients as well, age was not an exclusion criterion in our study, in contrast to other studies investigating frailty. Tumor recurrence or death led to exclusion from the analyses from that time point onwards (Fig. 1).

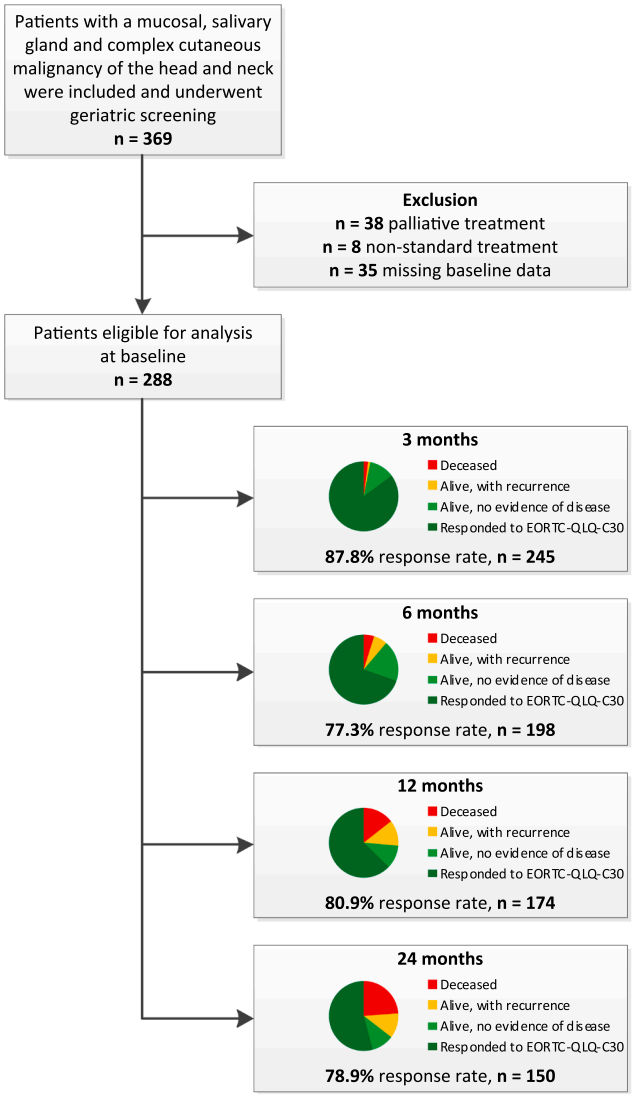

Fig. 1. Flowchart diagram with the in- and exclusion of patients and follow-up statistics of the analyzed cohort.

Data collection

Patients' age, sex, tumor site, histopathology, cancer stage, primary treatment and comorbidities were registered at baseline. Staging was done according to the seventh edition of the Union for International Cancer Control (UICC) TNM classification of malignant tumors [19]. Comorbidities were graded using the Adult Comorbidity Evaluation (ACE-27) as *none*, *mild*, *moderate* or *severe* [20]. As part of a geriatric screening at our outpatient clinic, within the scope of OncoLifeS, frailty status of patients was assessed using two validated frailty screening instruments. The Groningen Frailty Indicator (GFI), a fifteen-item questionnaire, was completed by patients either at the outpatient clinic or at home and returned by mail. Patients with a GFI score greater than or equal to four were considered frail [21]. The Geriatric 8 (G8), an eight-item scoring instrument, was completed by one of the investigators or a nurse together with the patient at the outpatient clinic. Patients with a G8 score lower than or equal to fourteen were considered as frail [22]. Although the intention of the study was purely observational, advancing insights of patients' frailty status might have unconsciously led to referral to a geriatrician.

As our primary measure of follow-up, patients were asked to report HRQoL using the European Organisation for Research and Treatment of

Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) before treatment and at three, six, twelve and twenty four months after treatment [23]. Global health status, functional scales, symptom scales and summary score were calculated according to the EORTC-QLQ-C30 scoring manuals [24,25].

Statistical analysis

All statistical procedures were performed with SPSS Statistics 23.0 software (IBM, Armonk, New York, United States of America). Descriptive statistics were presented as mean ± standard deviation (SD), median (interquartile range) or frequency (percentage). Differences between groups were analyzed with T-test for normally distributed continuous data and χ^2 test or Fisher's exact test for categorical data.

We employed Linear Mixed-effect Models (LMMs) for the analyses of repeated continuous measures, i.e. the EORTC-QLQ-C30 scales. LMMs are a superior method for analyzing large longitudinal datasets as they allow missing data points without discarding entire cases. An online available methods paper was used as a reference [26]. Typically, HRQoL decreases steeply during treatment, and then slowly tends to get better over time (Fig. 2a) [27]. Due to this irregular shape of trajectory, we only performed analysis on the three to twenty-four month interval, treating it as being linear (Fig. 2b). Leaving out polynomial terms makes interpreting coefficients possible and thus allows for assessing clinical relevance rather than a p-value.

For the analyses, covariance type was set to *unstructured*. Fixed effects included the *intercept* and at least the variables *time*, *frailty* and *frailty*time*. Coefficients for *frailty* refer to the difference in HRQoL for frail and non-frail patients at three months after treatment. Coefficients for the interaction term *frailty*time* refer to the effect of frailty on change of HRQoL over time (per year). Coefficients yielded 95% confidence intervals (CIs) and p-values. All models were adjusted for baseline differences between frail and non-frail patients, by adding the baseline score of dependent EORTC-QLQ-C30 scale to the model. Furthermore, all models were adjusted for age, sex, cancer stage, treatment modality and comorbidity as well as their interaction with time (coefficients not shown in table). For random effects an intercept was included for between subject differences and covariance type was *unstructured*. Estimation method was set to Maximum Likelihood (ML) and predicted values and standard error of predicted values were saved for graphs. Between models, model fit was compared using likelihood ratio testing.

Results

Patient characteristics

In this study, 288 patients were included. Follow-up and drop-out statistics are shown in Fig. 1. During follow-up, 84 patients developed recurrent disease and 66 patients died. Response rates for EORTC-QLQ-C30 remained stable throughout follow-up, averaging around 80%.

Patient characteristics are presented in Table 1. The mean age was 68.4 years and approximately two-thirds of patients were male. Most patients had mucosal cancer (79.5%), followed by skin malignancy (18.8%) and malignant salivary gland tumor (1.7%). Most patients (86.1%) had squamous cell carcinoma. The most common primary mucosal sites were oral cavity (25.7%), larynx (22.9%) and oropharynx (18.1%). Patients underwent either primary surgery (56.6%), radiotherapy (28.8%) or chemoradiation (14.6%), or a combination of those. According to the GFI, 29.3% of patients were frail, while using the G8, 54.7% were considered frail. Tumor site, histopathology, stage and treatment type did not differ between frail and non-frail patients; however, frail patients (both by GFI and G8) had significantly higher age and more severe comorbidity (Table 1).

Frailty is associated with decline in quality of life

Mean EORTC-QLQ-C30 scores at baseline and during follow-up are provided in Supplementary table 1 and 2. Frailty, measured by GFI was associated with significantly worse Global Health Status/Quality of Life

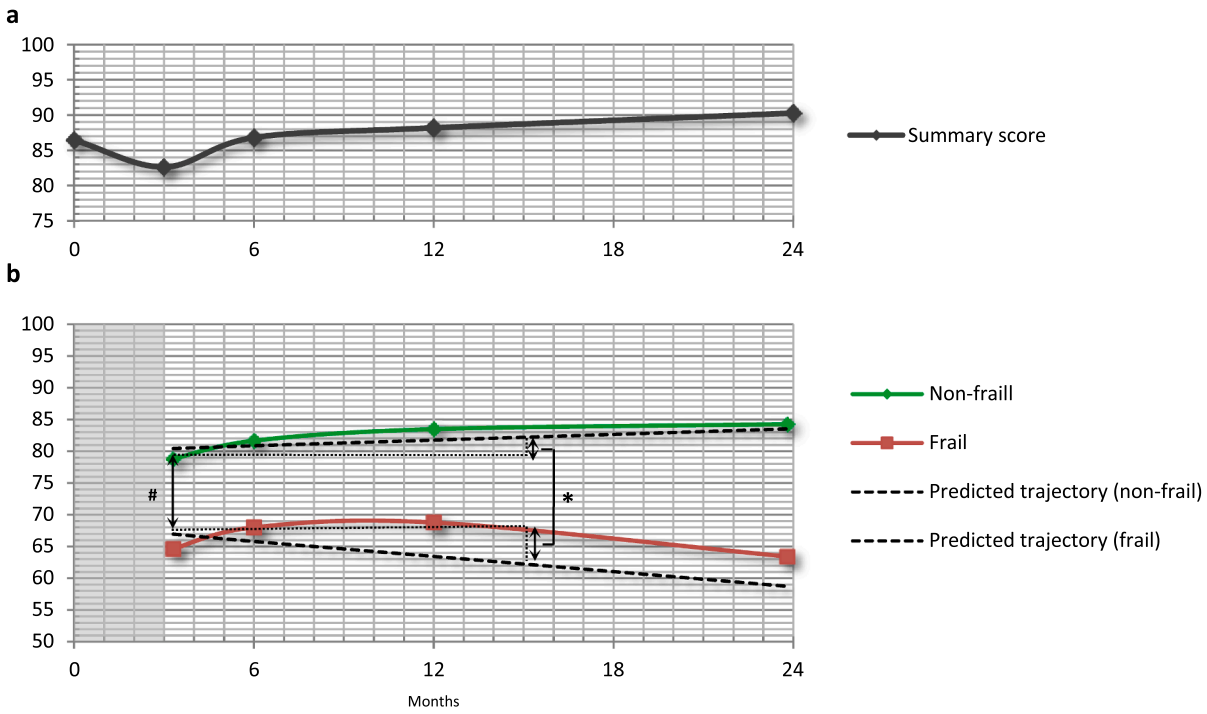

Fig. 2. Quality of life during and after treatment for head and neck cancer. (**a**) Mean summary EORTC-QLQ-C30 score: a typical shape of quality of life trajectory. (**b**) Example of Global health status/QoL trajectory for the interpretation of linear mixed model analysis. Green (non-frail patients) and red (frail patients) lines indicate means. Dashed lines indicate predicted trajectory by the linear mixed model. # Refers to the difference in quality of life at 3 months after treatment (*frail* estimate in the models). * Refers to the different course of quality of life trajectories for frail and non-frail patients with respect to 1 year (*frail*time* estimate in the models).

Table 1
Patient characteristics of the included cohort (n = 288). Values given as *n(%)* unless otherwise specified. *P-values* given for [a] *t*-test [b] χ^2 test or [c] Fisher's exact test. ACE-27 = Adult Comorbidity Evaluation 27.

Patient characteristics	**Groningen Frailty Indicator**			**Geriatric 8**			**Total (n = 288)**
Baseline	*Non-frail (n = 203)*	*Frail (n = 84)*	*p-value*	*Non-frail (n = 126)*	*Frail (n = 152)*	*p-value*	
Age							
Mean ± SD	67.2 ± 10.6	71.4 ± 11.2	**0.003**[a]	65.8 ± 9.6	70.4 ± 11.7	**0.001**[a]	68.4 ± 10.9
Median (interquartile range)	67.2 (59.6–75.4)	69.1 (62.5–80.7)		66.0 (59.4–73.3)	69.2 (62.4–79.4)		68.2 (60.6–76.7)
Sex							
Male	142 (70.0)	55 (65.5)	0.457[b]	95 (75.4)	96 (63.2)	**0.028**[b]	198 (68.8)
Female	61 (30.0)	29 (34.5)		31 (24.6)	56 (36.8)		90 (31.3)
Reason for referral							
Primary tumor	190 (93.6)	78 (92.9)	0.819[b]	117 (92.9)	143 (94.1)	0.680[b]	269 (93.4)
Recurrent tumor	13 (6.4)	6 (7.1)		9 (7.1)	9 (5.9)		19 (6.6)
Tumor site							
Oral cavity	52 (25.6)	22 (26.2)	0.377[c]	30 (23.8)	41 (27.0)	0.327[c]	74 (25.7)
Nasal cavity and paranasal sinus	13 (6.4)	2 (2.4)		8 (6.3)	7 (4.6)		16 (5.6)
Nasopharynx	4 (2.0)	0 (0.0)		3 (2.4)	1 (0.7)		4 (1.4)
Oropharynx	36 (17.7)	16 (19.0)		24 (19.0)	28 (18.4)		52 (18.1)
Hypopharynx	5 (2.5)	4 (4.8)		2 (1.6)	7 (4.6)		9 (3.1)
Larynx	44 (21.7)	22 (26.2)		36 (28.6)	29 (19.1)		66 (22.9)
Salivary glands	3 (1.5)	2 (2.4)		1 (0.8)	4 (2.6)		5 (1.7)
Skin	38 (18.7)	16 (19.0)		19 (15.1)	32 (21.1)		54 (18.8)
Unknown primary tumor	8 (3.9)	0 (0.0)		3 (2.4)	3 (2.0)		8 (2.8)
Histopathology							
Squamous Cell Carcinoma	172 (84.7)	76 (90.5)	0.196[b]	110 (87.3)	129 (84.9)	0.561[b]	248 (86.1)
Other	31 (15.3)	8 (9.5)		16 (12.7)	23 (15.1)		40 (13.9)
Stage							
I	51 (25.8)	20 (23.8)	0.987[b]	36 (28.6)	31 (21.1)	0.368[b]	71 (24.7)
II	40 (20.2)	18 (21.4)		27 (21.4)	28 (19.0)		58 (20.1)
III	28 (14.1)	12 (14.3)		15 (11.9)	24 (16.3)		40 (13.9)
IV	79 (39.9)	34 (40.5)		48 (38.1)	64 (43.5)		114 (39.6)
Primary treatment							
Surgery	117 (57.7)	45 (53.6)	0.455[b]	70 (55.6)	86 (56.6)	0.498[b]	163 (56.6)
Postoperative radiotherapy	42 (20.7)	18 (21.4)		22 (17.5)	38 (25.0)		61 (21.2)
Postoperative chemoradiation	4 (2.0)	1 (1.2)		3 (2.4)	2 (1.3)		5 (1.7)
Radiotherapy	53 (26.1)	30 (35.7)		35 (27.8)	45 (29.6)		83 (28.8)
Chemoradiation	33 (16.3)	9 (10.7)		21 (16.7)	21 (13.8)		42 (14.6)
ACE-27							
No comorbidity	55 (27.1)	7 (8.3)	**0.000**[b]	37 (29.4)	24 (15.8)	**0.000**[b]	62 (21.5)
Mild comorbidity	71 (35.0)	31 (36.9)		52 (41.3)	47 (30.9)		102 (35.4)
Moderate comorbidity	54 (26.6)	21 (25.0)		25 (19.8)	45 (29.6)		76 (26.4)
Severe comorbidity	23 (11.3)	25 (29.8)		12 (9.5)	36 (23.7)		48 (16.7)

(GHS/QoL) at three months after treatment (β = −8.70(−13.54;−3.86), p < 0.001), but also with a further decline of GHS/QoL during two years after treatment (β = −7.47(−11.23;−3.70), p < 0.001), in models adjusted for baseline and relevant covariates (Table 2 and Fig. 3a). Frailty measured by G8 was associated with worse GHS/QoL at three months after treatment (β = −6.68 (−11.00;−2.37), p = 0.003) as well, but not with a worse course over time (Table 2 and Fig. 3g).

Frailty is associated with decline in functioning

Frail patients, according to GFI, had worse physical (β = −4.55(−8.70;−0.40), p = 0.032), emotional (β = −10.92(−16.06;−5.79), p < 0.001) and social functioning (β = −8.44 (−13.91;−2.98), p = 0.003) at three months after treatment than their non-frail counterparts, adjusted for baseline and covariates (Table 2 and Fig. 3b,d,f). Moreover, these patients showed a significant further decline of physical (β = −3.28(−6.26;−0.31), p = 0.031) and role functioning (β = −7.27(−12.26;−2.28), p = 0.005) over time, compared to non-frail patients (Table 2 and Fig. 3b,c). When frailty was measured by G8, only emotional functioning (β = −5.02(−9.43;−0.73), p = 0.022) was different between frail and non-frail patients at three months after treatment (Table 2 and Fig. 3j).

Frailty is associated with increased symptom burden

Frail patients, measured by GFI, showed more fatigue (β = 8.25(2.15;14.36), p = 0.008), pain (β = 10.09(5.05;15.13), p < 0.001), dyspnea (β = 8.53(3.21;13.85), p = 0.002), insomnia (β = 8.07(1.35;14.79), p = 0.019), appetite loss (β = 14.23(−7.65;20.81), p < 0.001), diarrhea (β = 4.58(1.16;8.01), p = 0.009), and financial difficulties (β = 7.36(2.80;11.93), p = 0.002) than non-frail patients in models adjusted for baseline and relevant covariates, at three months after treatment (Table 2). Additionally, prolonged complaints of nausea and vomiting were seen in frail patients (β = 2.87(0.66;5.09), p = 0.011). Frailty, measured by the G8, was associated with more dyspnea (β = 5.02(0.14;9.90), p = 0.044), appetite loss (β = 7.21(1.03;13.39), p = 0.022), and diarrhea (β = 3.40(0.27;6.54), p = 0.033) at three months after treatment (Table 2).

Discussion

To our knowledge, this is the first study examining the association between frailty and changes in HRQoL after treatment in HNC patients. Key findings include that frailty, identified by two different frailty screening tools, was associated with a decline in QoL, different functioning domains, and increased symptom burden after treatment for HNC, independently of other relevant factors. Moreover, frailty at baseline was also associated with further deterioration of QoL and functioning during two years of follow-up. These findings emphasize

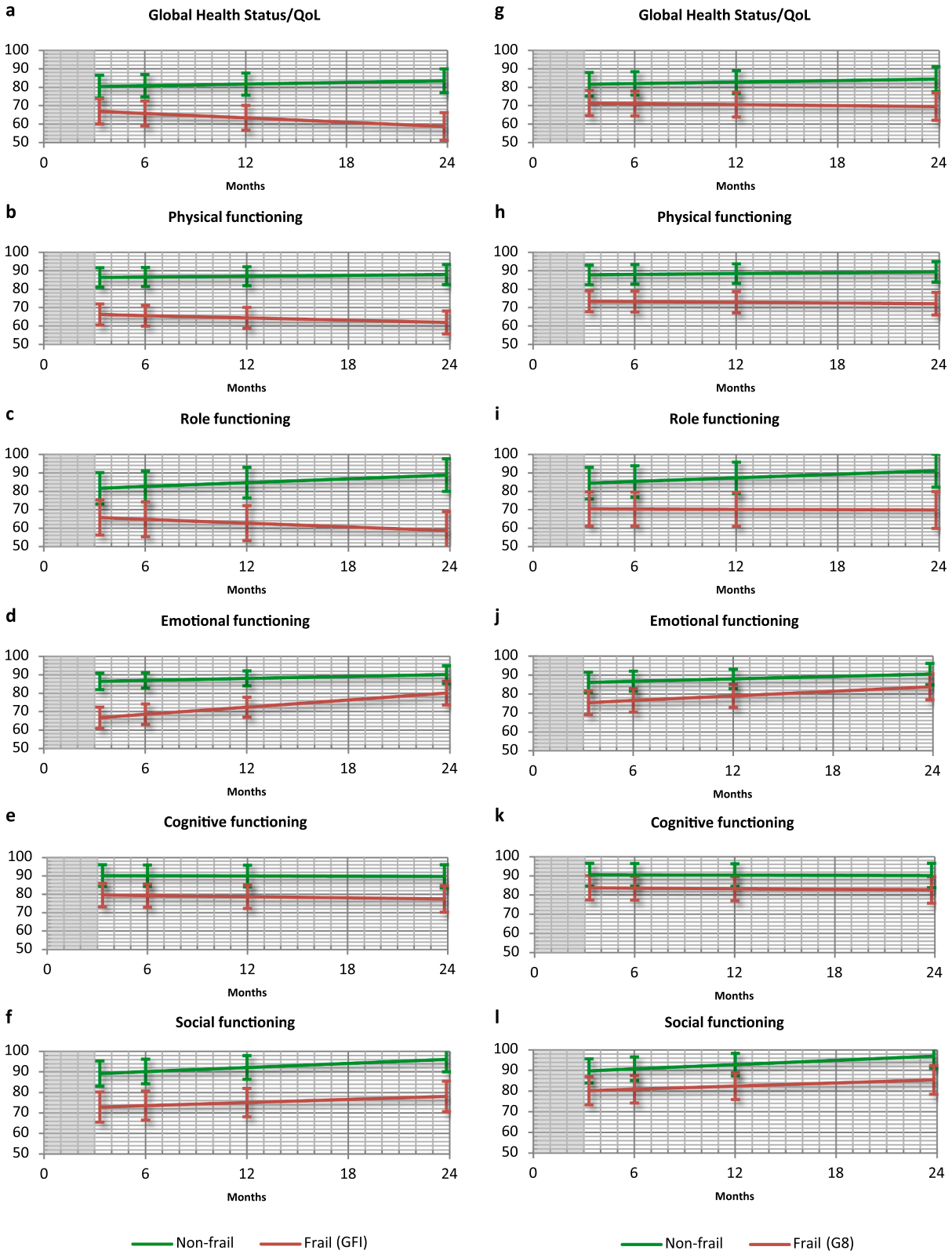

Fig. 3. Predicted values and standard error of predicted values by linear mixed models for EORTC-QLQ-C30 scales. **a-f** = frailty defined by Groningen Frailty Indicator. **g-l** = frailty defined by Geriatric 8.

Table 2
Results of linear mixed model analysis. Frailty measured by Groningen Frailty Indicator and Geriatric 8 alters quality of life after treatment. *Frail* refers to the main effect (difference in score of frail patients with respect to non-frail patients at 3 months). *Frail*Time* refers to the interaction of frailty and time, indicating the amount of change in Quality of Life over time (with respect to 1 year) for frail compared to non-frail patients. [a] All models were adjusted for baseline differences in corresponding EORTC-QLQ-C30 scale, and age, sex, stage, treatment modality and comorbidity and their interaction with time.

EORTC-QLQ-C30		Groningen Frailty Indicator [a]				Geriatric 8 [a]			
Scale	*Parameters*	*Estimate (β)*	*95% CI*		*p-value*	*Estimate (β)*	*95% CI*		*p-value*
Summary score	Frail	−6.12	−9.57	−2.67	< **0.001**	−2.87	−5.84	0.10	0.058
	Frail*Time	−1.70	−4.28	0.88	0.191	−0.74	−2.65	1.18	0.448
Global health status/QoL	Frail	−8.70	−13.54	−3.86	< **0.001**	−6.68	−11.00	−2.37	**0.003**
	Frail*Time	−7.47	−11.23	−3.70	< **0.001**	−2.39	−5.55	0.77	0.138
Functional scales									
Physical functioning	Frail	−4.55	−8.70	−0.40	**0.032**	−1.85	−5.43	1.74	0.311
	Frail*Time	−3.28	−6.26	−0.31	**0.031**	−1.36	−3.76	1.03	0.262
Role functioning	Frail	−5.70	−12.42	1.02	0.096	−5.31	−11.22	0.59	0.078
	Frail*Time	−7.27	−12.26	−2.28	**0.005**	−2.57	−6.49	1.36	0.198
Emotional functioning	Frail	−10.92	−16.06	−5.79	< **0.001**	−5.08	−9.43	−0.73	**0.022**
	Frail*Time	2.07	−2.45	6.60	0.367	0.41	−3.05	3.86	0.817
Cognitive functioning	Frail	−3.88	−8.13	0.37	0.074	−2.59	−6.38	1.20	0.180
	Frail*Time	−0.89	−4.31	2.54	0.610	−0.44	−3.29	2.41	0.761
Social functioning	Frail	−8.44	−13.91	−2.98	**0.003**	−2.78	−7.51	1.95	0.248
	Frail*Time	−2.73	−6.77	1.30	0.183	−2.68	−6.02	0.65	0.114
Symptom scales									
Fatigue	Frail	8.25	2.15	14.36	**0.008**	4.58	−0.90	10.07	0.101
	Frail*Time	3.59	−0.74	7.92	0.104	1.26	−2.23	4.75	0.475
Nausea and vomiting	Frail	1.46	−1.55	4.47	0.340	0.34	−2.42	3.10	0.809
	Frail*Time	2.87	0.66	5.09	**0.011**	2.13	−0.23	4.49	0.077
Pain	Frail	10.09	5.05	15.13	< **0.001**	4.57	−0.11	9.26	0.056
	Frail*Time	3.31	−1.53	8.15	0.178	0.03	−3.97	4.03	0.988
Dyspnoea	Frail	8.53	3.21	13.85	**0.002**	5.02	0.14	9.90	**0.044**
	Frail*Time	0.14	−4.01	4.30	0.946	0.49	−2.86	3.84	0.773
Insomnia	Frail	8.07	1.35	14.79	**0.019**	4.13	−1.76	10.03	0.169
	Frail*Time	−3.45	−8.91	2.01	0.214	−0.37	−4.87	4.12	0.871
Appetite loss	Frail	14.23	7.65	20.81	< **0.001**	7.21	1.03	13.39	**0.022**
	Frail*Time	−2.99	−8.29	2.31	0.267	−1.12	−5.61	3.37	0.623
Constipation	Frail	3.25	−1.26	7.77	0.157	0.01	−4.07	4.09	0.996
	Frail*Time	−0.25	−3.90	3.39	0.891	−0.53	−3.64	2.57	0.736
Diarrhoea	Frail	4.58	1.16	8.01	**0.009**	3.40	0.27	6.54	**0.033**
	Frail*Time	0.67	−3.13	4.46	0.730	0.08	−3.05	3.21	0.959
Financial difficulties	Frail	7.36	2.80	11.93	**0.002**	3.72	−0.47	7.91	0.082
	Frail*Time	0.89	−3.08	4.85	0.660	1.68	−1.62	4.98	0.315

the importance of implementing frailty screening in treatment counseling and decision making.

As we expected, frail patients showed worse GHS/QoL after treatment than non-frail patients, regardless of their baseline score, and age, sex, cancer stage, treatment modality and comorbidity. This was not only the case at three months after treatment, but their trajectory increasingly diverged from non-frail patients during the two years of follow-up. This effect was most pronounced when frailty was measured by using the GFI and may roughly be interpreted in two ways: either the frail patients' GHS/QoL trajectory deteriorates over time compared to non-frail patients, or recovery for frail patients is not as good as for non-frail patients. Plotted trajectories (Fig. 3a) reveal that this is a combination of both deterioration and worse recovery, however, this should be interpreted for each EORTC-QLQ-C30 scale independently.

Although only a minor difference (8.70 points) on the GHS/QoL scale between frail and non-frail patients was found at three months after treatment (Table 2, *frail* term), adding the increase per year (7.47 points, Table 2, *frail*time* term) resulted in a major cumulative difference (21.77 points) two years after treatment, which was adjusted for confounding factors. This is seen in plotted trajectories as well (Fig. 3a). According to classification of Osoba et al. (5–10 points difference should be interpreted as 'little' change, 10–20 points as 'moderate' change and > 20 as ' very much' change), the relative decrease in GHS/QoL is clinically highly relevant [28]. These findings could have a major impact on decision making: being aware of poorer outcomes for frail patients may and should be taken into account during shared decision making.

Comparing our results with published literature, a similar analysis

was recently performed by Kirkhus et al. in a heterogeneous oncological cohort [17]. Frailty, assessed using a modified geriatric assessment, was associated with worse GHS/QoL but not with further decline over time during twelve months follow-up [17]. However, this study did not adjust for baseline differences between frail and non-frail patients, which have been shown to be significant at baseline already [29]. This may explain the larger estimates than in our present study. Other studies that have addressed frailty with respect to GHS/QoL did not find significant differences in the breast cancer and colorectal cancer population [15,16]. Only one study included a small proportion of HNC patients (4.3%) and found within a frail population (based on G8) that several factors such as stage, pain, fatigue, nutrition and comorbidity were associated with decline in GHS/QoL [30]. Though, the study population was very heterogeneous, analyses were unadjusted for different treatment modalities and lacked long-term follow-up.

An important contributor to patients' HRQoL is the level of functioning. *Physical* functioning has been demonstrated to be worse in older patients after treatment for HNC [31]. In our study, after adjusting for age, frailty was associated with worse physical functioning both shortly after treatment as well as with further deterioration during follow-up. Literature data on this issue is heterogeneous [15–17,32], but most importantly, not investigated in HNC. Differences between cohort characteristics and research methodology may largely explain differences.

Role functioning is often overlooked in literature and rarely investigated as a primary outcome measure with respect to frailty. In our study, frailty (GFI) was strongly associated with decline in role functioning over time. When reviewing the EORTC-QLQ-C30 questions involved in role functioning *'Were you limited in doing either your work or other daily activities?'* and *'Were you limited in pursuing your hobbies or other leisure time activities?'*, these seem important matters for QoL.

Emotional functioning was significantly worse for frail (GFI and G8) patients three months after treatment. Since frailty is a multidimensional geriatric syndrome including a significant psychological domain as well, this was to be expected: patients with premorbid psychological issues have a higher risk of developing psychological problems during and after treatment [33]. Improvement of emotional functioning after treatment occurred in both frail and non-frail patients (Fig. 3d,j), despite the known high prevalence of fear of recurrence, depression and even high suicide risk in the HNC population in other studies [34–36].

Cognitive functioning was not significantly affected by treatment or by frailty during follow-up in our study. Another study investigating HNC patients treated with radiotherapy, however, did show significant decline of cognitive function within seven years after treatment [37]. Probably, their objective assessment of cognitive function is much more sensitive to cognitive alterations than the patient-reported cognitive functioning scale, employed in our study. These results should therefore be interpreted with care [38].

Social functioning is specifically at risk in HNC treatment due to the diseases' relation with the organs for communication [39,40]. We found frail (GFI) patients to have worse social functioning than non-frail patients shortly after treatment, but both groups gradually improved in the following years, similar to data in literature [41].

Clearly, large differences exist between screening tools such as GFI and G8. This leads to the question: which are the most important domains of a geriatric screening with respect to changes in QoL? G8 is known as a very physically oriented screening tool with more than half of the questions related to nutrition, weight loss and comorbidities [9]. G8 is strongly associated with surgical complications as well as survival in oncological cohorts, but the relation with HRQoL has rarely been investigated [42]. In our study, G8 showed a weaker association with HRQoL than GFI. The GFI covers larger functional and psychosocial domains of frailty [9] which are, apparently, superior in long-term patient reported outcomes. Some studies have already investigated separate domains of geriatric screening in relation to QoL in more heterogeneous oncological cohorts: one found comorbidity and nutrition to be associated with decline in QoL after three months and another showed associations of malnutrition [30], depression and impaired mobility with decline in QoL after six months [43].

It has been difficult to show the objective benefit of implementing a geriatric screening in standard oncological healthcare with outcomes such as adverse events, QoL or survival [44,45]. Though, it has been shown that treatment recommendations are significantly different when an onco-geriatric multidisciplinary team is involved in decision making [12]. This does not necessarily mean that we should stop treating frail patients. After all, frail patients do not regret the decision that was made more than non-frail patients [46], but identification of vulnerabilities may open doors to pre-treatment optimization or a more patient-tailored treatment plan. Prehabilitation studies are currently being carried out, also in the field of HNC.

The main strengths of this study include the prospective inclusion of a relatively large cohort, the use of well-known validated questionnaires to address frailty and HRQoL, and a notable two years of follow-up. Solid statistical analysis was performed handling missing data well and therefore limiting bias, and also controlling for baseline differences and confounders. Some limitations may be the relative heterogeneity of the cohort, which includes mucosal, salivary gland and cutaneous tumors, and possibly underrepresentation of the frailest patients. Inclusion of frail patients remains difficult due to refusal to participate, inability (being overburdened) to undergo geriatric screening or non-responses to questionnaires [47].

Conclusion

Frailty is significantly associated with decline in QoL and functioning after treatment for HNC and even further deterioration in the long-term. Screening for frailty is highly recommended in the HNC population, as it may have implications for decision making or pre-treatment optimization.

Declaration of Competing Interest

None.

Acknowledgements

None.

Funding sources

None.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2020.105020.

References

[1] Bray F, Soerjomataram I. The Changing Global Burden of Cancer: Transitions in Human Development and Implications for Cancer Prevention and Control. Cancer Dis. Control Priorities. 3rd ed., Washington D.C.: The International Bank for Reconstruction and Development / The World Bank; 2015. p. 23–44.

[2] Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet 2013;381:752–62. https://doi.org/10.1016/S0140-6736(12)62167-9.

[3] van Deudekom FJ, Schimberg AS, Kallenberg MH, Slingerland M, van der Velden LA, Mooijaart SP. Functional and cognitive impairment, social environment, frailty and adverse health outcomes in older patients with head and neck cancer, a systematic review. Oral Oncol 2017;64:27–36. https://doi.org/10.1016/j.oraloncology.2016.11.013.

[4] Bras L, Driessen DAJJ, de Vries J, Festen S, van der Laan BFAM, van Leeuwen BL, et al. Patients with head and neck cancer: Are they frailer than patients with other solid malignancies? Eur J Cancer Care (Engl) 2019:1–9. https://doi.org/10.1111/ecc.13170.

[5] Kurkcu M, Meijer RI, Lonterman S, Muller M. de van der Schueren MAE. The association between nutritional status and frailty characteristics among geriatric outpatients. Clin Nutr ESPEN 2018;23:112–6.
[6] Kojima G, Iliffe S, Walters K. Smoking as a predictor of frailty: a systematic review. BMC Geriatr 2015;15:131. https://doi.org/10.1186/s12877-015-0134-9.
[7] Strandberg AY, Trygg T, Pitkälä KH, Strandberg TE. Alcohol consumption in midlife and old age and risk of frailty. Age Ageing 2018;47:248–54. https://doi.org/10.1093/ageing/afx165.
[8] Soto-Perez-de-Celis E, Li D, Yuan Y, Lau YM, Hurria A. Functional versus chronological age: geriatric assessments to guide decision making in older patients with cancer. Lancet Oncol 2018;19:e305–16. https://doi.org/10.1016/S1470-2045(18)30348-6.
[9] Hamaker ME, Jonker JM, de Rooij SE, Vos AG, Smorenburg CH, van Munster BC. Frailty screening methods for predicting outcome of a comprehensive geriatric assessment in elderly patients with cancer: a systematic review. Lancet Oncol 2012;13:e437–44. 10.1016/S1470-2045(12)70259-0.
[10] Fu TS, Sklar M, Cohen M, de Almeida JR, Sawka AM, Alibhai SMH, et al. Is Frailty Associated With Worse Outcomes After Head and Neck Surgery? A Narrative Review. Laryngoscope 2019. https://doi.org/10.1002/lary.28307.
[11] Akishita M, Ishii S, Kojima T, Kozaki K, Kuzuya M, Arai H, et al. Priorities of Health Care Outcomes for the Elderly. J Am Med Dir Assoc 2013;14:479–84. 10.1016/j.jamda.2013.01.009.
[12] Festen S, Kok M, Hopstaken JS, van der Wal-Huisman H, van der Leest A, Reyners AKL, et al. How to incorporate geriatric assessment in clinical decision-making for older patients with cancer. An implementation study. J Geriatr Oncol 2019;10:951–9. 10.1016/j.jgo.2019.04.006.
[13] Stegmann ME, Festen S, Brandenbarg D, Schuling J, van Leeuwen B, de Graeff P, et al. Using the Outcome Prioritization Tool (OPT) to assess the preferences of older patients in clinical decision-making: A review. Maturitas 2019;128:49–52. 10.1016/j.maturitas.2019.07.022.
[14] de Arruda FN, Oonk MHM, Mourits MJE, de Graeff P, Jalving M, de Bock GH. Determinants of health-related quality of life in elderly ovarian cancer patients: The role of frailty and dependence. Gynecol Oncol 2019;153:610–5. 10.1016/j.ygyno.2019.03.249.
[15] Rønning B, Wyller TB, Nesbakken A, Skovlund E, Jordhøy MS, Bakka A, et al. Quality of life in older and frail patients after surgery for colorectal cancer-A follow-up study. J Geriatr Oncol 2016;7:195–200. https://doi.org/10.1016/j.jgo.2016.03.002.
[16] Williams GR, Deal AM, Sanoff HK, Nyrop KA, Guerard EJ, Pergolotti M, et al. Frailty and health-related quality of life in older women with breast cancer. Support Care Cancer 2019;27:2693–8. https://doi.org/10.1007/s00520-018-4558-6.
[17] Kirkhus L, Šaltytė Benth J, Grønberg BH, Hjermstad MJ, Rostoft S, Harneshaug M, et al. Frailty identified by geriatric assessment is associated with poor functioning, high symptom burden and increased risk of physical decline in older cancer patients: Prospective observational study. Palliat Med 2019;33:312–22. https://doi.org/10.1177/0269216319825972.
[18] Sidorenkov G, Nagel J, Meijer C, Duker JJ, Groen HJM, Halmos GB, et al. The OncoLifeS data-biobank for oncology: A comprehensive repository of clinical data, biological samples, and the patient's perspective. J Transl Med 2019;17:1–9. https://doi.org/10.1186/s12967-019-2122-x.
[19] Sobin LH, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumours. 7th ed. Oxford, UK: Wiley-Blackwell; 2009.
[20] Piccirillo JF. Importance of comorbidity in head and neck cancer. Laryngoscope 2000;110:593–602. https://doi.org/10.1097/00005537-200004000-00011.
[21] Schuurmans H, Steverink N, Lindenberg S, Frieswijk N, Slaets JPJ. Old or Frail: What Tells Us More? J Gerontol Ser A Biol Sci Med Sci 2004;59:M962–5. https://doi.org/10.1093/gerona/59.9.M962.
[22] Delva F, Bellera CA, Mathoulin-Pélissier S, Rainfray M, Mertens C, Fonck M, et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. Ann Oncol 2012;23:2166–72. https://doi.org/10.1093/annonc/mdr587.
[23] Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European organization for research and treatment of cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–76. https://doi.org/10.1093/jnci/85.5.365.
[24] Fayers P, Aaronson N, Bjordal K, Groenvold M, Curran D, Bottomley A. The EORTC QLQ-C30 Scoring Manual. 3rd ed. Brussels: European Organisation for Research and Treatment of Cancer; 2001.
[25] EORTC study group. Scoring summary score C30 2013;89:2006.
[26] Shek DTL, Ma CMS. Longitudinal data analyses using linear mixed models in SPSS: concepts, procedures and illustrations. Scient World J 2011;11:42–76. https://doi.org/10.1100/tsw.2011.2.
[27] Roick J, Danker H, Dietz A, Papsdorf K, Singer S. Predictors of changes in quality of life in head and neck cancer patients: a prospective study over a 6-month period. Eur Arch Oto-Rhino-Laryngology 2020;277:559–67. https://doi.org/10.1007/s00405-019-05695-z.
[28] Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 1998;16:139–44. https://doi.org/10.1200/JCO.1998.16.1.139.
[29] Kojima G, Iliffe S, Jivraj S, Walters K. Association between frailty and quality of life among community-dwelling older people: a systematic review and meta-analysis. J Epidemiol Commun Health 2016;70:716–21. https://doi.org/10.1136/jech-2015-206717.
[30] Decoster L, Quinten C, Kenis C, Flamaing J, Debruyne PR, De Groof I, et al. Health related quality of life in older patients with solid tumors and prognostic factors for decline. J Geriatr Oncol 2019;10:895–903. https://doi.org/10.1016/j.jgo.2019.03.018.
[31] Van Der Schroeff MP, Derks W, Hordijk GJ, De Leeuw RJ. The effect of age on survival and quality of life in elderly head and neck cancer patients: A long-term prospective study. Eur Arch Oto-Rhino-Laryngology 2007;264:415–22. https://doi.org/10.1007/s00405-006-0203-y.
[32] Decoster L, Kenis C, Schallier D, Vansteenkiste J, Nackaerts K, Vanacker L, et al. Geriatric Assessment and Functional Decline in Older Patients with Lung Cancer. Lung 2017;195:619–26. https://doi.org/10.1007/s00408-017-0025-2.
[33] Cook SA, Salmon P, Hayes G, Byrne A, Fisher PL. Predictors of emotional distress a year or more after diagnosis of cancer: A systematic review of the literature. Psychooncology 2018;27:791–801. https://doi.org/10.1002/pon.4601.
[34] Mirosevic S, Thewes B, van Herpen C, Kaanders J, Merkx T, Humphris G, et al. Prevalence and clinical and psychological correlates of high fear of cancer recurrence in patients newly diagnosed with head and neck cancer. Head Neck 2019;41:3187–200. https://doi.org/10.1002/hed.25812.
[35] Korsten LHA, Jansen F, de Haan BJF, Sent D, Cuijpers P, Leemans CR, et al. Factors associated with depression over time in head and neck cancer patients: A systematic review. Psychooncology 2019;28:1159–83. https://doi.org/10.1002/pon.5058.
[36] Zeller JL. High Suicide Risk Found for Patients With Head and Neck Cancer. JAMA 2006;296:1716–7. https://doi.org/10.1001/jama.296.14.1716.
[37] Wilbers J, Kappelle AC, Versteeg L, Tuladhar AM, Steens SCA, Meijer FJA, et al. Cognitive function, depression, fatigue and quality of life among long-term survivors of head and neck cancer. Neuro-Oncology Pract 2015;2:144–50. https://doi.org/10.1093/nop/npv012.
[38] Klepstad P, Hilton P, Moen J, Fougner B, Borchgrevink PC, Kaasa S. Self-reports are not related to objective assessments of cognitive function and sedation in patients with cancer pain admitted to a palliative care unit. Palliat Med 2002;16:513–9. https://doi.org/10.1191/0269216302pm587oa.
[39] Callahan C. Facial Disfigurement and Sense of Self in Head and Neck Cancer. Soc Work Health Care 2005;40:73–87. https://doi.org/10.1300/J010v40n02_05.
[40] Kaplan BE, Hurley FL. Head and neck cancer: a threat to life and social functioning. Soc Work Health Care 1979;5:51–8. https://doi.org/10.1300/J010v05n01_06.
[41] Ringash J, Bernstein LJ, Devins G, Dunphy C, Giuliani M, Martino R, et al. Head and Neck Cancer Survivorship: Learning the Needs, Meeting the Needs. Semin Radiat Oncol 2018;28:64–74. 10.1016/j.semradonc.2017.08.008.
[42] van Walree IC, Scheepers E, van Huis-Tanja L, Emmelot-Vonk MH, Bellera C, Soubeyran P, et al. A systematic review on the association of the G8 with geriatric assessment, prognosis and course of treatment in older patients with cancer. J Geriatr Oncol 2019;10:847–58. 10.1016/j.jgo.2019.04.016.
[43] Kirkhus L, Harneshaug M, Benth JŠ, Grønberg BH, Rostoft S, Bergh S, et al. Modifiable factors affecting older patients' quality of life and physical function during cancer treatment. J Geriatr Oncol 2019;10:904–12. 10.1016/j.jgo.2019.08.001.
[44] Jeppesen SS, Matzen L-E, Brink C, Bliucukiene R, Kasch S, Schytte T, et al. Impact of comprehensive geriatric assessment on quality of life, overall survival, and unplanned admission in patients with non-small cell lung cancer treated with stereotactic body radiotherapy. J Geriatr Oncol 2018;9:575–82. https://doi.org/10.1016/j.jgo.2018.05.009.
[45] Nadaraja S, Matzen L-E, Jørgensen TL, Dysager L, Knudsen AØ, Jeppesen SS, et al. The impact of comprehensive geriatric assessment for optimal treatment of older patients with cancer: A randomized parallel-group clinical trial. J Geriatr Oncol 2019;S1879–4068(19):30124–9. https://doi.org/10.1016/j.jgo.2019.06.019.
[46] Thomas CM, Sklar MC, Su J, Xu W, De Almeida JR, Gullane P, et al. Evaluation of Older Age and Frailty as Factors Associated with Depression and Postoperative Decision Regret in Patients Undergoing Major Head and Neck Surgery. JAMA Otolaryngol - Head Neck Surg 2019:1–8. https://doi.org/10.1001/jamaoto.2019.3020.
[47] Hempenius L, Slaets JPJ, Boelens MAM, van Asselt DZB, de Bock GH, Wiggers T, et al. Inclusion of frail elderly patients in clinical trials: Solutions to the problems. J Geriatr Oncol 2013;4:26–31. 10.1016/j.jgo.2012.08.004.